

## REVIEW

# Relationships between the amyloid precursor protein and its various proteolytic fragments and neuronal systems

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**Abstract**

Alzheimer's disease (AD) is a progressive neurodegenerative disease and in its familial form is associated with mutations in the amyloid precursor protein (APP) and the presenilins (PSs). Much data regarding the interactions of APP, its proteolytic fragments and PS have been generated, expanding our understanding of the roles of these proteins in mechanisms underlying cognitive function and revealing many complex relationships with wide ranging cellular systems. In this review, we examine the multiple interactions of APP and its proteolytic fragments with other neuronal systems in terms of feedback loops and use these relationships to build a map. We highlight the complexity involved in the APP proteolytic system and discuss alternative perspectives on the roles of APP and its proteolytic fragments in dynamic processes associated with disease progression in AD. We highlight areas where data are missing and suggest potential confounding factors. We suggest that a systems biology approach enhances representations of the data and may be more useful in modelling both normal cognition and disease processes.

**Introduction**

Alzheimer's disease (AD) is a clinico-pathological diagnosis in which progressive neurodegenerative disease is associated with the dementia syndrome. Neuropathologically, AD is generally characterised as including deposits of amyloid beta protein (A $\beta$ ) in senile and neuritic plaques [1] and neurofibrillary tangles of paired helical filaments of hyperphosphorylated tau [2,3]. Currently, AD is classified as familial AD, which has an early age of onset and is associated with mutations in

either the amyloid precursor protein (APP) or the presenilins (PSs), and sporadic AD, which has a later age of onset and a less clear aetiology [4,5]. Down's syndrome, with an extra copy of APP on chromosome 21, also leads to a form of AD with increasing age. The genetic data associated with familial AD [6] strongly suggest that PS, APP and its proteolytic fragment A $\beta$  are involved in AD disease progression but exactly how they contribute to both normal cognition and dementia is the focus of much debate.

Many non-genetic factors also appear to affect disease initiation and progression, including diet, exercise and education, and many models have been proposed to account for their roles in AD. Population studies (for example, the Medical Research Council Cognitive Function and Aging Study [7]) demonstrate that vascular and AD-associated pathologies are common in people with and without any clinical manifestation of dementia. Coupled with data suggesting that the relationship between amyloid pathology and dementia attenuates with age [8], this suggests that sporadic AD especially has a complex disease aetiology [9].

Many models of disease progression have been proposed to account for the accumulating data on AD. These models form the basis of experimental design and affect how findings are interpreted. Data relevant to disease progression in AD are accumulating from many diverse fields, including neuropsychology, brain imaging, molecular biology and genetics. Integrating these data is becoming harder as expertise is required in so many areas.

The pre-eminent model of the last few decades has been the amyloid cascade hypothesis [10-12], based on genetic data and the role of PS in the proteolysis of APP to release the 39 to 43 residue A $\beta$ . This model proposes that overproduction of A $\beta$ , or an increase in A $\beta_{(1-42)}$  relative to A $\beta_{(1-40)}$ , is causal in the disease process. In this model, A $\beta$ , perhaps in a specific aggregation state, is proposed as neurotoxic. An alternative interpretation of data relating to APP, PS and A $\beta$  is the presenilin hypothesis [13], where loss or altered function of PS is proposed as the causal factor in disease progression.

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Other models suggest different initiating factors, such as cholesterol [14], mitochondria and apoptosis [15], insulin signalling and energy metabolism [16,17], cholinergic insufficiency [18],  $\text{Ca}^{2+}$  deregulation [19,20], signalling decoherence [21] or a combination of multiple factors (for example, [22,23]). No single model adequately explains how APP, PS, cholesterol and other factors interact with synaptic plasticity, learning and memory in normal and disease states. This suggests that models currently in use in AD research require re-evaluation.

Recent approaches to integrating the data relevant to AD have involved the use of text mining, bioinformatic databases and network analysis for gene co-expression and protein-protein interactions [24-33]. Studies using automated interrogation of genomic and proteomic databases, such as UNIPROTKB [34], NCBI Entrez Gene [35], and IntAct [36], and text mining in literature databases such as Pubmed [37] have confirmed the involvement of many previously highlighted neurological processes, extended the connectivity between known molecular targets and revealed new targets for investigation (summarised in Table 1).

Understanding how APP contributes to synaptic plasticity is important in understanding normal cognition and disease progression in AD. Here, we approach the process of integrating the available data relating to the relationships between APP and its proteolytic fragments and neuronal processes based on a systems biology approach and build a map of relationships. We are not aiming to define protein interactions nor find new targets for investigation, but to highlight relationships in the existing literature that illustrate the complexity involved and how this relates to our current understanding of the role of APP in AD. We highlight areas where data are missing and predict relationships that may confound current disease models.

### Building the map

Relationships involving APP and each of its proteolytic fragments were identified from literature searches using relevant key words. Each interaction identified was manually entered into a non-hierarchical network using the mapping software Compendium [38]. This software allowed each molecule or neuronal system to be represented as a node within the map. Each node in the map could contain further networks of nodes, leading to a multi-dimensional organisation of information. These further nodes represented information relevant to the molecule of the parent node and could include notes describing possible relevance, questions raised and links to relevant entries on various bioinformatic databases. The map is not meant to be read as a protein-protein interaction network (PPI), but rather was designed to summarise and collate information relevant to the APP

system in a more general way. Physiological outcomes, such as changes in signalling, were included, even though the precise molecular interactions are not clear. Any additional details, such as new biological relationships or new molecular interactions, can be added as they arise. Relationships between molecules are represented by connectors, with annotation if required. Figure 1 shows a limited map built in this way from references cited in the text, with additional references listed in Table 2.

Unlike more automated network studies such as that by Perreau and colleagues [25] where nodes were included in the network only if there was direct evidence of molecular interaction, or various studies [30-33] where co-expression criteria were applied, no specific criteria were imposed and any relationship found was included. Known differences in peptide behaviour (for example, [39,40]) necessitated separate nodes for  $\text{A}\beta_{(1-40)}$  and  $\text{A}\beta_{(1-42)}$ . This was extended systematically to include all the peptide fragments, including  $\text{P3}_{(17-40)}$ ,  $\text{P3}_{(17-42)}$ , secreted APP (sAPP) $\alpha$  and sAPP $\beta$  (the extracellular amino-terminal fragments following  $\alpha$ - and  $\beta$ -cleavage, respectively), C31, and so on to take account of any potential behavioural differences. This is in contrast to various network constructions where the various proteolytic fragments are collapsed into an APP parental node, possibly reflecting the UNIPROTKB identifier (P05067) being the same for each peptide. Additionally, different aggregation states of each of the peptides (monomers, dimers, oligomers or fibrils) were considered separately. These additional details have been omitted from Figure 1 for clarity. Since there was little or no evidence for many of the  $\text{A}\beta$ -type peptides [41], these were collapsed into a separate node (not shown).

The relationships in Figure 1 were analysed manually by identifying feedback loops. Direct feedback loops were defined as relationships between APP, any of its proteolytic fragments and any other molecule or functional change that was represented at more than one point in the map. Possible indirect feedback loops between any neural system, such as neurotransmitter signalling,  $\text{Ca}^{2+}$  homeostasis or the inflammation cascade, were also investigated by looking for molecules or functional change in these systems that interact with APP or any of its proteolytic fragments at more than one point in the map.

Following a brief summary of APP cleavage, two examples of the relationships between APP pathways and neuronal processes, looking at the extracellular matrix (ECM) and endocytosis, serve to illustrate the implications of the complexity involved.

### The amyloid precursor protein

#### Overview

APP is a type I transmembrane protein [42] with a large extracellular amino-terminal domain, a transmembrane

**Table 1. Overview of protein-protein interaction network studies**

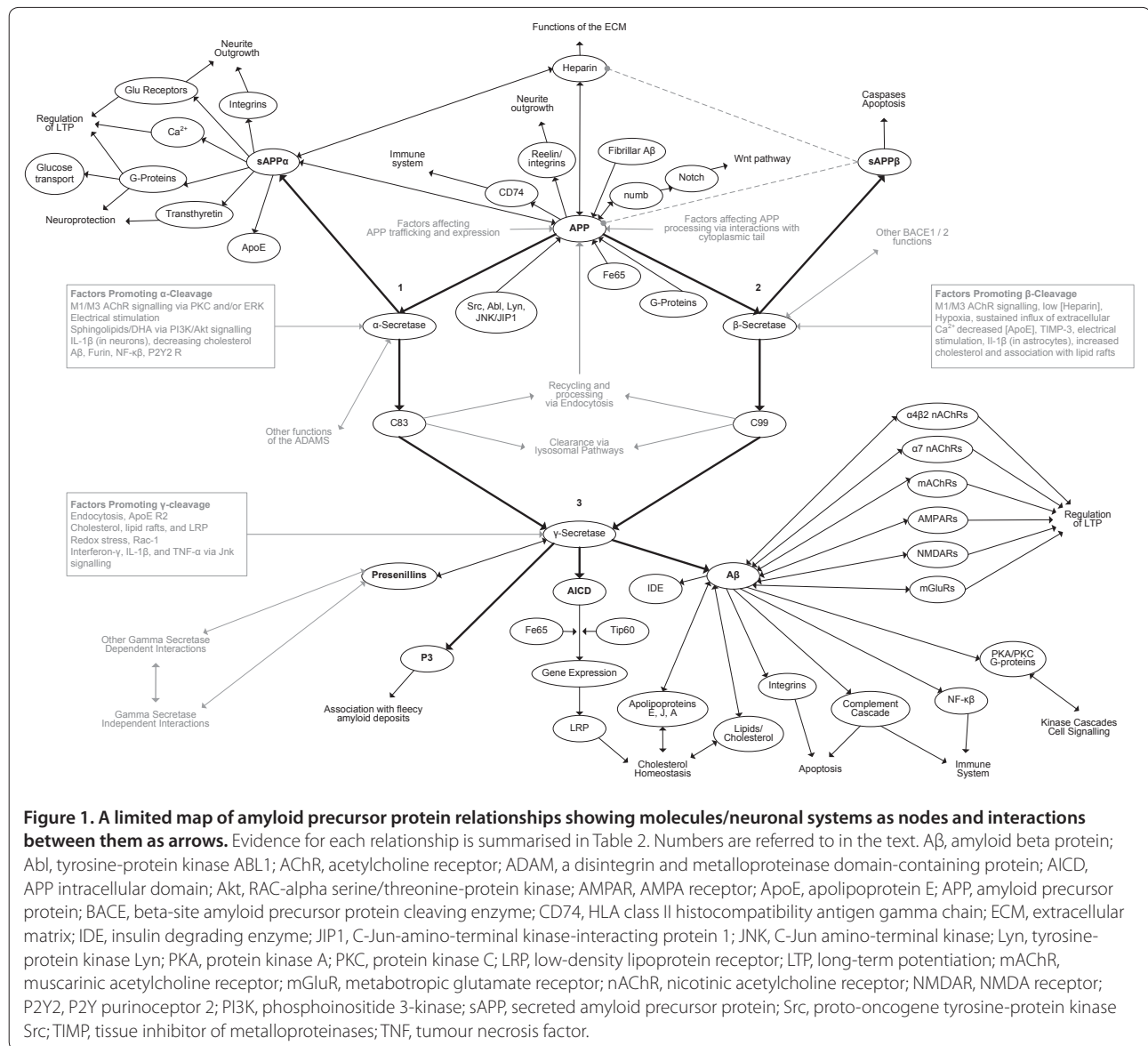
| Reference | Selection criteria                                                                                                                                                                  | Exclusion criteria                                                                                                                                                                                                                   | Main focus                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| [25]      | Evidence of direct interaction between molecules from literature searches                                                                                                           | Metals, non-protein molecules, poorly characterised proteins, specific peptides are included as parent genes                                                                                                                         | Direct PPI involving APP and associated fragments by domain with reference to APP770 isoform but with application to all isoforms; molecular networks with reference to biological processes                                                                                                                                                                                                                                                                                                                               |
| [33]      | Twelve causative or susceptibility 'seed' genes previously associated with AD; candidate genes were selected due to close proximity to GWAS-identified gene loci associated with AD | Proteins lacking open reading frames; transcription factors, highly glycosylated proteins, extracellular proteins, proteins containing several transmembrane regions; co-expression data were used as a filter                       | Identification of genes in AD with reference to direct PPI and biological processes                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| [31]      | Co-expressed genes that differ between controls and AD                                                                                                                              | Probe-sets not mapping to any gene or mapping to hypothetical proteins were removed                                                                                                                                                  | Variations in transcriptomes of AD suggest similarities with molecular networks associated with CVD and diabetes. <i>Cis</i> -regulatory elements identified in several diseases known to co-occur with AD                                                                                                                                                                                                                                                                                                                 |
| [30]      | Genes with variable expression between an AD and an aging microarray study                                                                                                          | Arrays that significantly varied between subjects in each study group; outlier removal, unreliable probe sets defined as being present in three or fewer arrays; control probe sets and probes not associated with known genes       | Transcriptional changes between AD and aging highlight possible contributors to disease pathways. Many biological processes are shared between AD and aging. Many novel associations found, including MAPK pathways and unknown proteins. New functional and disease related association for PSEN1 with glial/neuronal interactions; confirms and highlights gamma14.3.3 signalling in AD                                                                                                                                  |
| [32]      | Genes with variable expression between human and mouse from brain sample microarray gene expression data sets                                                                       | Outlier removal, filtered (method not specified) to remove datasets with low interspecies expression or low connectivity correlations; only top 5,000 Human and 3,000 Mouse connected genes included, rest removed to reduce 'noise' | Mouse and human networks are highly similar with expression levels more preserved than connectivity. Significant species difference in: i) co-expression arrays from astroglia and microglia but not neurons; ii) the role of PSEN1 in oligodendrocytes and myelination; and iii) further evidence of species difference in glial cells linked to neuroinflammation in human AD. Neuronal death is a small part of the biological changes associated with AD in this dataset; new transcription factors associated with AD |
| [27]      | All AD and related pathways in KEGG database with co-expression data                                                                                                                | Genes without corresponding data in the assembled PPI network and proteins with no corresponding genes in the co-expression data                                                                                                     | Crosstalk between pathways involved in AD; close relationships between APP and apoptosis, Notch, Wnt pathways and cytokine-cytokine interactions in this dataset, brain areas vary in specific pathway relationships and order of significance                                                                                                                                                                                                                                                                             |

AD, Alzheimer's disease; APP, amyloid precursor protein; CVD, cardiovascular disease; GWAS, genome-wide association study; KEGG, Kyoto Encyclopedia of Genes and Genomes; MAPK, mitogen-activated protein kinase; PPI, protein-protein interaction; PSEN, presenilin.

domain and an intracellular carboxy-terminal domain that resembles a cell surface receptor [43]. It is expressed in several isoforms, with APP<sub>695</sub> the main isoform expressed by neurons. APP has a high turnover, with a half life ranging from approximately 1 hour [44-46] to approximately 4 hours [47-49]. In addition to its functions at the cell surface, full length mature APP is also processed via competing pathways that release proteolytic fragments [5,43,50] (recently reviewed in [51]). In effect there are four possible routes: APP may remain functionally active at the cell surface; it may be internalised and recycled or degraded; it may be cleaved via the  $\alpha$ -pathway, releasing the sAPP $\alpha$  fragment, leaving the membrane bound C83 carboxy-terminal fragment that is further processed to the P3 fragment; or it may be cleaved via the  $\beta$ -pathway releasing sAPP $\beta$ , leaving the membrane bound C99 carboxy-terminal fragment that is further processed to the A $\beta$  fragment.

As can be seen in Figure 1,  $\alpha$ - and  $\beta$ -cleavage pathways (numbered 1 and 2, respectively) converge on a further intramembrane  $\gamma$ -cleavage (numbered 3) by the PS-containing  $\gamma$ -secretase complex to release the variable length A $\beta$  and P3 peptides and the variable length APP intracellular domain (AICD). Additional cleavages, including caspase cleavage of the carboxyl terminus at residue D664 of APP<sub>695</sub>, producing the alternative length carboxy-terminal fragment C31 [51], and cleavage by BACE2 (beta-site amyloid precursor protein cleaving enzyme 2) within the A $\beta$  sequence [52], have been omitted for clarity.

Unprocessed APP is degraded or recycled via the endosomal or lysosomal pathways and may be recycled back to the membrane and processed within approximately 30 minutes [46], with perhaps a third to a half being processed via the cleavage pathways as measured by secreted sAPP $\alpha$ / $\beta$  [46]. Regulatory relationships



promoting expression or cleavage have been collapsed into summary boxes in Figure 1 for simplicity.

### Complex feedback pathways involving APP and its proteolytic fragments; the extracellular matrix and endocytosis

#### The extracellular matrix

APP interacts with itself and its own proteolytic fragments at many points in the network with various functional consequences. At the cell surface, the large amino-terminal domain of full length APP interacts with many components of the ECM, including heparins and heparin sulphate proteoglycans [42], laminin, collagen [53,54] and β-1-integrin [43,55,56], and contributes to early neuronal development, axon and neurite growth,

cell adhesion and synaptic plasticity [43,57]. Many of these interactions are now represented in MatrixDB [58], an ECM interaction database.

The amino-terminal domain of APP binds heparin in a pH- and zinc-dependant manner and this binding promotes the formation of APP homodimers [42,59-61]. Depending on various factors, including cell compartment and pH, this dimerisation may influence APP proteolysis via α- or β-cleavages due to conformational changes [59], though this requires further investigation.

The large amino-terminal fragment released by α-cleavage, sAPPα, is a soluble monomer. It retains two heparin binding sites and has been shown to bind heparin as a dimer [60]. The ability of sAPPα to disrupt APP dimerisation at the cell surface is thought to contribute to

**Table 2. Additional references supporting the network diagram in Figure 1**

| Factor                      | Details                                                                                                                                                                                                                                                                                                                               | Reference    |
|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| Akt                         | Aβ increases Akt phosphorylation in the short term via a mechanism involving α7-nAChR and NMDARs, with phosphorylation levels returning to baseline over the long term                                                                                                                                                                | [99]         |
| AMPA receptors              | AMPA glutamate receptor density is reduced by Aβ oligomers via reduction of CamKII                                                                                                                                                                                                                                                    | [100,101]    |
| ApoE                        | Decreased levels of ApoE lead to increased β-cleavage                                                                                                                                                                                                                                                                                 | [102]        |
|                             | ApoE promotes polymerisation of Aβ into fibrils and enhances fibrillar Aβ deposition in neuritic plaques. The high affinity binding of Aβ to ApoE reduces ability of ApoE to bind lipids                                                                                                                                              | [103-105]    |
| Ca <sup>2+</sup>            | sAPPα modulates Ca <sup>2+</sup> signalling by activating high conductance K <sup>+</sup> channels via a mechanism dependent on cGMP                                                                                                                                                                                                  | [106]        |
| CD74                        | Interacts with APP and reduces expression of Aβ                                                                                                                                                                                                                                                                                       | [107]        |
| Cholesterol                 | Interactions of cholesterol and APP may allow APP to react to cholesterol status of the cell                                                                                                                                                                                                                                          | [108]        |
|                             | Membrane cholesterol correlates with β-secretase activity and inhibition of β-secretase activity leads to increased membrane cholesterol levels. Moderate reductions in cholesterol enhance the co-expression of APP and BACE1 and promote the production of Aβ                                                                       | [109,110]    |
|                             | Aβ binds lipids and has high affinity for cholesterol. Aggregated Aβ <sub>(1-40)</sub> may affect lipid transport. Aβ binds 24-hydroxycholesterol and affects membrane choline carriers                                                                                                                                               | [111,112]    |
| Complement cascade          | Aβ activates neuronal complement cascade to induce the membrane attack complex and reduces complement regulatory proteins, increasing complement-mediated cytotoxicity                                                                                                                                                                | [113]        |
| Dishevelled                 | Dvl-1 increases sAPPα production mediated via JNK and PKC/MAPK but not via p38 MAPK                                                                                                                                                                                                                                                   | [114]        |
| Electrophysiology           | Hippocampal and cortical electrophysiological processes are modulated by sAPPα                                                                                                                                                                                                                                                        | [115]        |
|                             | Aβ <sub>(1-40)</sub> suppresses epileptiform activity in hippocampal neurons                                                                                                                                                                                                                                                          | [116]        |
| Fe65                        | APP binds Fe65 at the YENPTY sequence with effects on gene transcription, cytoskeleton and cell motility. Binding of Fe65 to APP is dependent on phosphorylation state of Y <sub>682</sub> ; phosphorylation of T <sub>668</sub> reduces the binding of Fe65 to YENPTY. Binding of Fe65 reduces Aβ                                    | [117-121]    |
| Furin                       | Furin enhances cleavage to active forms of ADAM10 and ADAM17, leading to enhanced α-cleavage                                                                                                                                                                                                                                          | [122]        |
| Glucose/glutamate transport | sAPPα enhances transport of glucose and glutamate in synapses and protects from oxidative stress via a mechanism involving cGMP                                                                                                                                                                                                       | [123]        |
| Glutamate signalling        | sAPPα suppresses NMDA currents rapidly and reversibly at concentrations of approximately 0.011 nM, possibly involving cGMP and a protein phosphatase. Reductions in sAPPα lead to reduced tetanically induced NMDA currents while increased sAPPα increased these currents and enhanced LTP                                           | [124,125]    |
| G-protein signalling        | Aβ directly increases TNF-α at high levels and at low levels increases TNF-α release by altering GPCR signalling at early stages of disease progression by indirect effects on GPCR kinase 2/5                                                                                                                                        | [126]        |
|                             | Full length and processed APP can potentially interact with G proteins via the cytoplasmic tail and this can be altered by APP mutations around the G protein binding site. This interaction has the potential to alter G-protein signalling with wide ranging effects, including Ca <sup>2+</sup> regulation and cell cycle pathways | [127-129]    |
| HDL                         | Aβ binds ApoA-I, ApoA-II, ApoE and ApoJ; binding modulates Aβ solubility                                                                                                                                                                                                                                                              | [130]        |
| Heparins                    | Proteolysis of immature BACE1 to its mature active form is promoted by low concentrations of heparin and inhibited at higher concentrations. Certain heparin derivatives may act as inhibitors of BACE1 and have therapeutic potential                                                                                                | [70,131,132] |
| IL-1β                       | Enhanced α-cleavage by ADAM10/17 via up-regulation of P2Y2 receptors and may increase levels of ADAM10/17 by approximately threefold                                                                                                                                                                                                  | [133,134]    |
|                             | Increases expression of APP and β-cleavage in astrocytes                                                                                                                                                                                                                                                                              | [135]        |
| Insulin degrading enzyme    | Aβ competes with insulin for IDE and reduced IDE availability may contribute to dementia                                                                                                                                                                                                                                              | [136]        |
| Integrins                   | sAPPα competes with APP for binding sites on integrin-β-1 and promotes neurite outgrowth                                                                                                                                                                                                                                              | [137]        |
|                             | Aβ binds focal adhesion molecules and integrins and modulates integrin/FA signalling pathways involved in cell cycle activation and cell death. The αv integrin subunit is required for Aβ-associated suppression of LTP                                                                                                              | [138,139]    |
| Lipids                      | Binding of Aβ to acidic lipid molecules promotes Aβ aggregation. Aβ binds membrane gangliosides, sphingolipids and cholesterol, which enhance Aβ aggregation                                                                                                                                                                          | [140-142]    |
|                             | Association of APP and BACE1 with lipid rafts increases Aβ                                                                                                                                                                                                                                                                            | [143]        |
|                             | Aβ endocytosis may also involve lipid rafts                                                                                                                                                                                                                                                                                           | [144]        |
|                             | Sphingolipids enhance α-cleavage via MAPK/ERK signalling                                                                                                                                                                                                                                                                              | [145]        |

*Continued overleaf*



**Table 2. Continued**

| Factor                                   | Details                                                                                                                                                                                                                                                                                                                                                                        | Reference    |
|------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| LTP                                      | Aβ suppresses LTP in hippocampal neurons via a mechanism involving α4β2 nAChRs; Aβ affects cascades downstream of NMDA GluR signalling                                                                                                                                                                                                                                         | [146,147]    |
| Muscarinic ACh signalling                | Increases in mAChR-M1 and -M3 activation upregulate α-cleavage via PKC activation. Muscarinic upregulation of sAPPα secretion may involve the activation of a Src tyrosine kinase, leading to activation of PKCα and ERK1/2. Increased M2 activation decreases sAPPα secretion                                                                                                 | [75,148-151] |
|                                          | Inhibition of muscarinic signalling promotes APP processing via β-pathway. Increased M1/M3 signalling promoted β-cleavage via PKC; MEK/ERK and increased expression of BACE1; M2 activation suppressed BACE expression                                                                                                                                                         | [152,153]    |
| MAPK/ERK signalling                      | MAPK cascade may mediate the independent effects of PKC and tyrosine kinase in human astrocytes                                                                                                                                                                                                                                                                                | [154]        |
| Neurite outgrowth                        | APP enhances neurite outgrowth independently from sAPPα                                                                                                                                                                                                                                                                                                                        | [155]        |
| NF-κB                                    | May reduce expression of BACE1                                                                                                                                                                                                                                                                                                                                                 | [156]        |
|                                          | NF-κB upregulation by capacitive Ca <sup>2+</sup> entry enhances sAPPα release via mAChR signalling                                                                                                                                                                                                                                                                            | [157]        |
| Nicotinic ACh signalling                 | Aβ <sub>(1-40)</sub> and Aβ <sub>(1-42)</sub> reduced A4β2 nAChR and α7 nAChR currents. Aβ <sub>(1-40)</sub> but not Aβ <sub>(1-42)</sub> increased glutamatergic AMPA. Signalling via A4β2 nAChR is associated with reduced Aβ                                                                                                                                                | [40,158]     |
|                                          | Aβ has high affinity for the α7 nAChR and this may be associated with increased Aβ accumulation. Differential effects of Aβ <sub>(1-40)</sub> and Aβ <sub>(1-42)</sub> on α7 nAChR as seen by different effects on ACh release and Ca <sup>2+</sup> influx. Disruption of signalling by α7 nAChR may be associated with Aβ-mediated increases in pre-synaptic Ca <sup>2+</sup> | [39,159,160] |
|                                          | Aβ <sub>(1-42)</sub> has approximately 5,000-fold greater affinity for α7 nAChR than for A4β2 nAChR                                                                                                                                                                                                                                                                            | [161]        |
| NMDA GluR                                | Aβ promotes endocytosis of NMDARs in cortical neurons with the involvement of protein phosphatase 2B and the tyrosine phosphatase STEP                                                                                                                                                                                                                                         | [162]        |
| Nucleotide signalling via P2Y2 receptors | G-protein-coupled purine receptor, P2Y2 enhanced the release of sAPPα in a time- and dose-dependent manner; probably mediated via ADAM10 and ADAM17                                                                                                                                                                                                                            | [163]        |
| numb                                     | APP binds numb when Y <sub>682</sub> is unphosphorylated and inhibits Notch signalling                                                                                                                                                                                                                                                                                         | [164]        |
| PKA/CREB                                 | Aβ inhibits PKA via increased persistence of its regulatory subunit PKAIIα, resulting in reduced CREB phosphorylation in response to glutamate                                                                                                                                                                                                                                 | [73]         |
| PKC                                      | PKC activators enhance α-cleavage                                                                                                                                                                                                                                                                                                                                              | [165,166]    |
|                                          | Aβ inhibits PKC                                                                                                                                                                                                                                                                                                                                                                | [167]        |
| Reelin                                   | Reelin interacts with APP and A3/β1-integrins and promotes neurite extension; APP endocytosis is reduced. Reelin signalling opposes the actions of Aβ                                                                                                                                                                                                                          | [56,168]     |
| Src, Abl, Lyn, JNK/JIP1                  | These tyrosine kinases bind to APP when phosphorylated at Y <sub>682</sub> with affinity increased by phosphorylation of T <sub>668</sub> . JNK phosphorylation of APP at T <sub>668</sub> modulated by JIP1                                                                                                                                                                   | [169,170]    |
| TIMP-3                                   | Increases in TIMP-3 led to decreased surface expression of ADAM10 and APP. The production of Aβ and CTF is increased. TIMP-3 appears to promote endocytosis and β-secretase cleavage                                                                                                                                                                                           | [171]        |
| Transthyretin                            | Neuroprotection in transgenic mice over-expressing mutant APP is associated with elevated levels of transthyretin and sAPPα and may be linked to increased proteolysis of Aβ                                                                                                                                                                                                   | [172,173]    |

Aβ, amyloid beta protein; ACh, acetylcholine; ADAM, a disintegrin and metalloproteinase domain-containing protein; Akt, RAC-alpha serine/threonine-protein kinase; AMPA, 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid; ApoE, apolipoprotein E; APP, amyloid precursor protein; CamKII, calcium/calmodulin-dependent protein kinase II; CD74, HLA class II histocompatibility antigen gamma chain; CREB, cyclic adenosine monophosphate response element-binding; CTF, carboxy-terminal fragment; ERK, extracellular signal-regulated kinase; FA, fatty acids; GluR, glutamate receptor; GPCR, G-protein-coupled receptor; HDL, high-density lipoprotein; IDE, insulin degrading enzyme; JIP1, C-Jun-amino-terminal kinase-interacting protein 1; JNK, C-Jun amino-terminal kinase; LTD, long-term depression; LTP, long-term potentiation; Lyn, tyrosine-protein kinase Lyn; MAPK, mitogen-activated protein kinase; mAChR, muscarinic acetylcholine receptor; MEK, ERK activator kinase; nAChR, nicotinic acetylcholine receptor; NMDAR, NMDA receptor; P2Y2, P2Y purinoceptor 2; PKA, protein kinase A; PKC, protein kinase C; sAPP, secreted amyloid precursor protein; Src, proto-oncogene tyrosine-protein kinase Src; TIMP, tissue inhibitor of metalloproteinases.

its neuroprotective actions [62-64] and may partly explain why sAPPα is approximately 100 times more neuroprotective against excitotoxicity, glucose deprivation and the addition of Aβ in hippocampal cultures than sAPPβ, which lacks the second carboxy-terminal heparin binding site [63]. Dementia status has been associated with both reduced sAPPα levels in cerebrospinal fluid [65] and an increased half life of sAPPα [49].

Differing by only 16 carboxy-terminal residues, sAPPα and sAPPβ share a high degree of sequence homology

and have the potential to compete with each other for binding sites. Since both sAPPβ and sAPPα are constantly present in the ECM in dynamically changing ratios, we predict that sAPPβ could act as an antagonist of sAPPα/APP (shown in Figure 2 as competitive inhibition (line 1)), with the potential to modulate various interactions between APP and sAPPα and the ECM. We predict, therefore, that any functional outcome from the interactions of the APP pathway will depend on the synergy between APP and its amino-terminal fragments.

A $\beta$  interacts with heparins in the ECM and at high levels may prevent the catabolism of proteoglycans and promote amyloid formation [66]. Reciprocally, heparins modulate many of the interactions involving A $\beta$ . Heparins enhance both nucleation and elongation processes in the aggregation of A $\beta$  [67] and modulate interactions of A $\beta$ ; for example, heparins can limit the neurotoxic and pro-inflammatory activity of A $\beta$  in a dose-dependent manner [68]. Additionally, heparins contribute to the uptake of A $\beta$  by a pathway shared with apolipoprotein E [69] and also contribute to the regulation of the  $\beta$ -secretase BACE in a dose-dependent manner, with low concentrations promoting and high concentrations inhibiting the activation of BACE1 [70].

In terms of direct feedback, A $\beta$  may be part of a negative feedback loop involved in the regulation of APP expression and the promotion of  $\alpha$ -cleavage. Fibrillar forms of various proteins, including A $\beta$ , interact with amino-terminal APP and increase APP expression [71] (Figure 2, line 2) and A $\beta_{(1-40)}$  may up-regulate expression of  $\alpha$ -secretase via integrin receptors and matrix metalloproteinase-9 activity [72] (Figure 2, line 3). Additionally, A $\beta$  has many indirect negative feedback relationships with  $\alpha$ -cleavage - for example, A $\beta$  inhibits protein kinase C [73] and insulin signalling [74], both involved in up-regulation of  $\alpha$ -cleavage [75] (Figure 2, line 5) - and additionally may negatively feedback on APP expression and its own production via a pathway involving Fe65 and glycogen synthase kinase 3 [76]. Reciprocally, changes to gene expression by sAPP $\alpha$  via the activation of NF- $\kappa$ B may attenuate the interactions of A $\beta$  [77] and this can be understood as reciprocal indirect feedback from the  $\alpha$ -pathway on the  $\beta$ -pathway (Figure 2, line 4).

The data reviewed above suggest that A $\beta$  may contribute to both direct and indirect feedback loops in the ECM at multiple points, with consequences for the interactions of APP, sAPP $\alpha$ , A $\beta$  and sAPP $\beta$  that may ultimately affect cell adhesion, neurite outgrowth and synaptic plasticity. These effects will depend on the specific sequence length, concentration and aggregation state of the A $\beta$ -type peptides, which may dynamically change in response to the neuronal environment.

### Endocytosis

Increases in endocytosis, often associated with synaptic activity, lead to both an increase in A $\beta$  [78] and a reduction in  $\alpha$ -cleavage and lower secreted sAPP $\alpha$  levels [79]. This may reflect the regulatory role of compartmentation in APP proteolysis, where  $\alpha$ -cleavage occurs at the cell surface and A $\beta$  production is associated with factors that promote endocytosis. No studies could be found investigating the role of endocytosis on P3 production, so this cannot be discussed specifically. Endocytosis allows a degree of dissociation between the  $\alpha$ - and  $\beta$ -cleavages

and  $\gamma$ -cleavage, resulting in levels of sAPP $\alpha$  and sAPP $\beta$  that may be independent of A $\beta_{(1-40/42)}$  and P3 levels, respectively. This means that in terms of function, APP processing via the  $\beta$ -pathway has the potential to either: modulate actions of sAPP $\alpha$  via competition with sAPP $\beta$ ; or modulate the actions of sAPP $\alpha$  and initiate actions mediated by A $\beta$ .

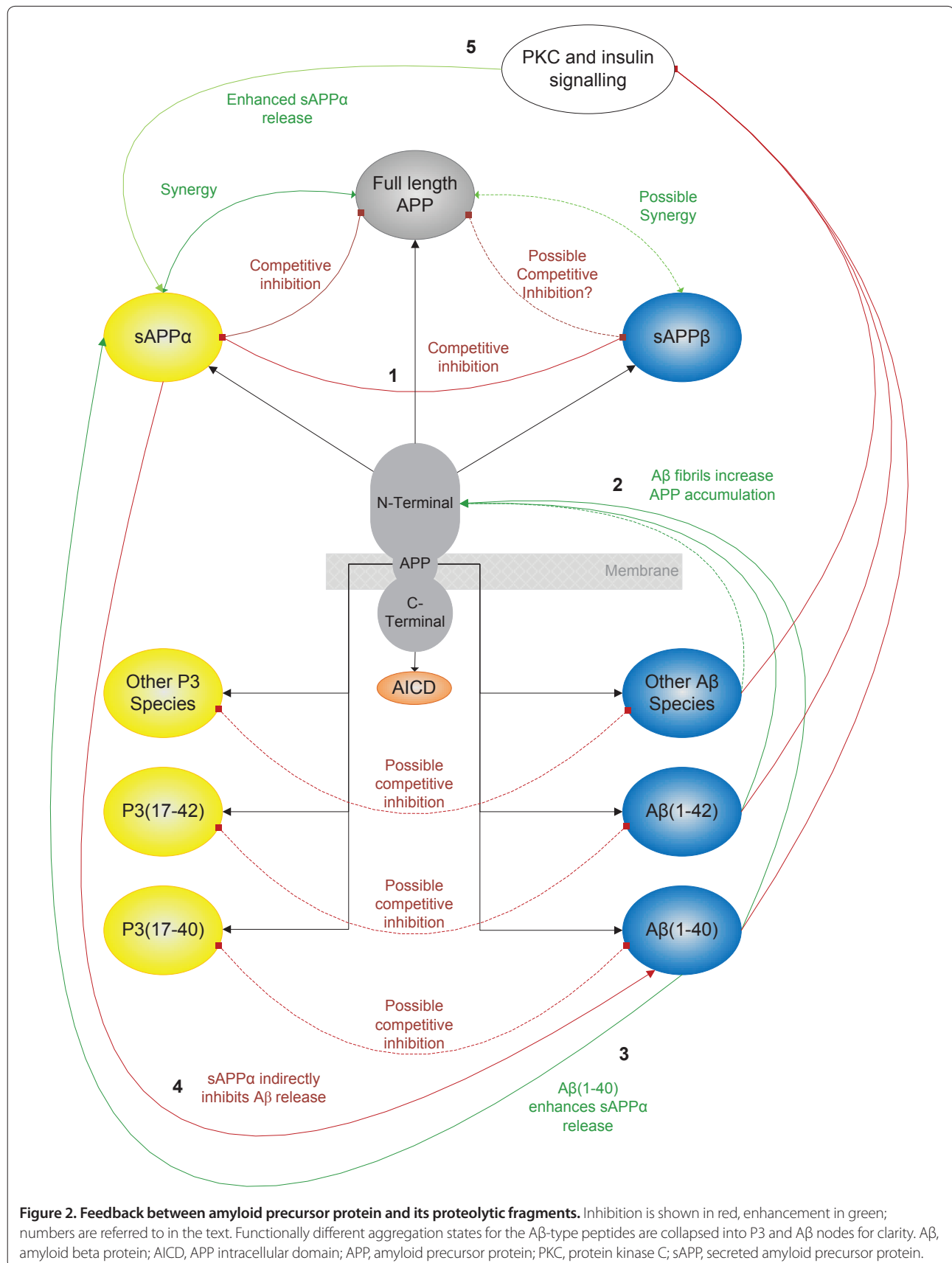
P3 corresponds to A $\beta_{(17-40/42)}$  and we predict that this shared sequence could allow P3 to modulate the interactions of A $\beta$  (shown in Figure 2 as competitive inhibition), especially where those interactions involve the carboxy-terminal amino acids. While no studies can be found that address this particular question directly, various amino-terminal truncated forms of A $\beta$  have been associated with diffuse plaques [80,81] and the A $\beta_{(17-40)}$  fragment, corresponding to P3, has been studied in terms of aggregation [82]. It is clear that amino-truncated A $\beta$  peptides, including P3, have potential for aggregation and can interact with A $\beta$ , but how this affects the physiological behaviour of neuronal systems is not clear. In terms of functional flow through the APP pathway, processing via the  $\alpha$ -pathway to release sAPP $\alpha$  and P3 could either: initiate actions of sAPP $\alpha$ ; or initiate actions of sAPP $\alpha$  and modulate actions mediated by A $\beta$ .

In terms of modelling these interactions in functional contexts, PPI networks may require a more detailed approach, where each sequence length and aggregation state is represented as an individual node.

### The effects of concentration, sequence length aggregation state and affinity

A $\beta$  is produced in a range of sequence lengths [41] and can form monomers, dimers, oligomers and fibrils. The amount of A $\beta$  produced is regulated and can dynamically change in response to many factors, including increased cholesterol [83], increased synaptic activity [84], heparins via activation of BACE1 [70], reduced acetylcholine (ACh) signalling via muscarinic receptors [70], sustained increased cytosolic Ca<sup>2+</sup> [85], and hypoxia [86]. Changes in concentration are a well recognised mechanism of regulation in cellular processes; for example, A $\beta_{(1-40)}$  and A $\beta_{(1-42)}$  both promote angiogenesis at nanomolar concentrations but inhibit it at higher micromolar concentrations [87].

Different sequence lengths show different behaviours; for example, A $\beta_{(1-42)}$  is more prone to aggregation than A $\beta_{(1-40)}$  due to a more rigid carboxyl terminus [88]. A $\beta$  monomers appear to have structured and unstructured regions, with differences in aqueous conformations between A $\beta_{(1-40)}$  and A $\beta_{(1-42)}$  [89]. While both A $\beta_{(1-40)}$  and A $\beta_{(1-42)}$  reduced currents via  $\alpha$ 7 and  $\alpha$ 4 $\beta$ 2 ACh receptors (AChRs), only A $\beta_{(1-40)}$  increased glutamatergic signalling via AMPA receptors [40]. Another study found that the





effects of  $A\beta_{(1-40)}$  and  $A\beta_{(1-42)}$  on  $\alpha 7$  AChRs, as measured by ACh release and  $Ca^{2+}$  influx, were different [39]. Additionally,  $A\beta_{(1-40)}$  may protect neurons from the effects of  $A\beta_{(1-42)}$  by disrupting the aggregation of  $A\beta_{(1-42)}$  [90] and this raises the possibility that P3-type peptides may act in similar ways. The functional effects of sequence length are only just beginning to be elucidated and should be expanded to include all the  $A\beta$ -type peptides, including P3. In addition to differences in peptide sequence and concentration, aggregation state also modulates function.  $A\beta$  oligomers appear to be spherical [91,92] and  $A\beta$  fibrils appear as fine fibres [92].  $A\beta$  oligomers, but not monomers or fibrils, enhance lipid release [93] and at low concentrations enhance neuronal differentiation [92] whereas  $A\beta$  fibrils, but not monomers or oligomers, may interact with APP and increase its expression [71]. While both soluble and aggregated forms of  $A\beta_{(1-40)}$  inhibit long-term potentiation, the fibrillar forms may additionally affect neurotransmitter release [94].

Within a specific cellular compartment, whether one interaction is more likely to occur than another depends on the relative affinities of the reactants involved. While dissociation constants have been measured for some reactions in rodent models (for example,  $K(i)$  values of  $A\beta_{(1-42)}$  for  $\alpha 7$  nicotinic AChRs from rat and guinea pig are 4.1 and 5.0 pM, respectively, and the  $K(i)$  of  $A\beta_{(1-42)}$  with  $\alpha 4\beta 2$  AChRs is approximately 5,000-fold lower at 30 and 23 nM, respectively [95]), we are missing dissociation constants for most interactions in humans.

Taken together, the data discussed above suggest that the interactions of APP and its proteolytic fragments with synaptic systems are complex and involve subtle changes in the relative ratios between APP and all its fragments. Given the complexity of the APP system, multiple neuronal systems have the potential to regulate the expression and proteolysis of APP and could also initiate imbalance within this system, leading to multiple possible disease pathways.

This complexity has the potential to confound purely empirical studies into the behaviour of the peptides in model systems. Over-expressing  $A\beta$  peptides in, for example, mouse models without knowing their concentrations, sequences and aggregation states and the background concentrations, sequences and aggregation states of the other relevant peptides in the experimental system that is being studied means that we do not know if the experimental results obtained are due to the properties of the  $A\beta$  peptides themselves or reflect a disrupted balance in a complex system over time, or perhaps both. While this distinction may seem subtle, given the self-organising and self-referencing properties of the human brain, an approach based on the principles in systems biology may better represent the roles of the APP pathway in functional contexts.

## Discussion

It is not possible to include the full extent of the known interaction of APP and its proteolytic fragments here and further interactions may yet be discovered. Data relating to the roles of APP and its proteolytic fragments in synaptic plasticity and AD have accumulated from many diverse fields and these need to be placed into context. One way of doing this is to investigate the relationships between APP, its proteolytic fragments and wider neuronal systems by mapping networks of interactions.

It is interesting that the networks generated in the various studies reviewed in Table 1 do not always overlap and different studies highlight different pathways or biological processes, for example,  $Fe^{2+}$  [28], apoptosis [96], or cardiovascular disease/diabetes [31]. Each study has different starting points, inclusion/exclusion criteria and network construction methods, so this lack of agreement is no surprise. It is difficult to assess the degree to which the various starting points, criteria and network construction methods bias results towards an outcome.

The study by Soler-Lopez and colleagues [33] may not model the interactions of full length APP in the membrane adequately, as many of the ECM proteins that might be expected to interact are excluded due to difficulties involved in expressing them in the experimental microarray used. This may shift the focus of their network more towards intracellular interactions. Given the importance of the various interactions of APP with components of the ECM, any study excluding such proteins and proteoglycans could be seriously confounded.

While the study by Perreau and colleagues [25] maps PPIs to specific domains of full length APP, they do not distinguish between the different proteolytic peptides. Additionally, transient interactions and biologically essential post-translational modifications, such as glycosylation and phosphorylation, cannot yet be fully represented in PPI networks [27], severely limiting the modelling of regulation and control in these models.

Studies comparing mouse and human gene expression networks [32] or aging and AD pathways [30] have revealed interesting results. Perhaps most striking is the study revealing a human-specific network for PS function in oligodendrocytes and myelination, with the potential to confound the current approach to modelling AD in rodents [32]. Miller and colleagues [30,32] also show important contributions from both neuronal and glial pathways, perhaps reflecting the contributions of glia to disease pathways found in humans [97,98]. The differences found in networks between glia and neurons could be extended to differentiate between specific neuronal types and future network models may usefully investigate why cholinergic neurons in AD appear more susceptible to degeneration than others.

We do not yet have totally inclusive, gene co-expression or PPI models of APP and related pathways to the level of detail required and this places limitations on their interpretation. Given the limitations, however, network studies do show the usefulness of the systems biology approach in integrating huge volumes of data and a simple search of patents in Google with the terms 'protein interaction network Alzheimer disease' retrieves more than 700 applications based on this approach. Network studies highlight the idea that multiple processes are involved in AD disease pathways, reveal new targets for further investigation and have generated new hypotheses. Network models have the potential to avoid biases inherent in other approaches, such as the emphasis on A $\beta$  in animal models based on the more reductionist amyloid cascade hypothesis, and allow multiple disease pathways to be represented in a single model, perhaps better relating to the processes involved in human disease.

We have suggested that APP and its proteolytic fragments appear to dynamically modulate each other by multiple mechanisms with evidence for both direct and indirect feedback loops between A $\beta$ , sAPP $\alpha$ , sAPP $\beta$  and full length APP. Additionally, the fragments derived from  $\gamma$ -cleavage, including the variable length fragments, P3 and A $\beta$ , have the potential to interact with each other and modulate multiple neuronal processes in subtle and dynamic ways. Unfortunately, evidence for the role(s) of P3 is almost entirely missing from the literature and that for sAPP $\beta$  is limited. Without this information, we cannot have a full picture of the contributions of the APP proteolytic system to normal neuronal processes and how these change during disease progression.

Given the number and range of reciprocal feedback relationships that APP and its proteolytic fragments are involved in, the effects of perturbing the APP proteolytic system may be better understood as dynamic, synergistic actions involving multiple players. A wide range of neuronal processes have the potential to interact with and regulate APP processing, allowing APP to monitor the current state of the cell. The multiple proteolytic pathways allow APP to assimilate signals from wide-ranging cellular systems and pass these signals on via the ratios of APP fragments. The constant turnover of APP contributes to the ability of neurons to sense the current state of the cell and use this information to set in motion future responses. The potential for subtly different signals both from the  $\alpha$ - and  $\beta$ -pathways via alternative peptides and the complex feedback relationships between them described above fits well with the fine control required for integrating neuronal systems.

The predicted synergy between APP and all its proteolytic fragments implies that the ratios of full length APP and all the various fragments, not just A $\beta_{(1-40)}$  and

A $\beta_{(1-42)}$ , are more important than absolute levels in coordinating neuronal responses. The complexity of the relationships described here has the potential to confound purely empirical investigations into the activities of any one proteolytic fragment studied in isolation. To avoid these predicted confounding effects, experimental approaches should be extended to account for the different concentrations, affinities and aggregation states of each peptide length, and experimental systems should be followed over time for each biological process in a systematic manner. With over 40 A $\beta$ -type peptides [41], this presents a challenge.

Generating useful network models will require a more detailed and comprehensive approach to experimental design, involving a range of experimental controls to account for all the confounding factors. These data will be essential for generating network models that are truly relevant to our understanding of normal and abnormal processes in the context of the human population.

#### Abbreviations

A $\beta$ , amyloid beta protein; ACh, acetylcholine; AChR, acetylcholine receptor; AD, Alzheimer's disease; APP, amyloid precursor protein; BACE, beta-site amyloid precursor protein cleaving enzyme; ECM, extracellular matrix; IL, interleukin; NF, nuclear factor; PPI, protein-protein interaction; PS, presenilin; sAPP, secreted amyloid precursor protein.

#### Competing interests

The authors declare that they have no competing interests.

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#### Author contributions

SH wrote the paper in discussion and with contributions from CB.

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